

Association of hiccup and SARS-CoV-2 infection with the administration of dexamethasone: a case report

Victoria Birluțiu^{1,*}, Ciprian Radu Șofariu²

Abstract

Introduction Among the less common symptoms associated with the SARS-CoV-2 infection the attention is drawn by a persistent hiccup that was recently quoted in the literature.

Case report We present the case of a 46-year-old Caucasian male patient hospitalized in the Infectious Diseases Clinic of the Academic Emergency Hospital Sibiu, Romania with laboratory confirmation of SARS-CoV-2 infection with a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay from nasopharyngeal swabs, that during the disease course developed persistent hiccup associated with the administration of cortisone therapy, dexamethasone. A decision to stop the treatment with cortisone preparations was made, with the disappearance of the hiccup after 36 hours.

Conclusions From our experience, other cases of SARS-CoV-2 infection that we managed during these months of the pandemic, with mild or severe forms of the disease, showed hiccup under treatment with dexamethasone, an event also described in other medical conditions under the same treatment and improved at its cessation or when replaced by methylprednisolone.

Keywords SARS-CoV-2 infection, hiccup, COVID-19, dexamethasone.

Introduction

SARS-CoV-2 infection was initially associated with standard symptomatology - fever, dyspnea, dry cough, and in dynamics with digestive manifestations - nausea, diarrhea, vomiting, anosmia, ageusia, neurological or cardiovascular manifestations. Subsequently, there were cases of COVID-19 that associated at the beginning or during the disease course micturition syncope,^{1,3} viral exanthema,^{4,7} psychiatric and thromboembolic manifestations, etc. Among the

less common symptoms, the attention is drawn by the persistent hiccup recently quoted in the literature.⁸ We present the case of a COVID-19 patient hospitalized in the Infectious Diseases Clinic of the Academic Emergency Hospital Sibiu, Romania with laboratory confirmation of SARS-CoV-2 infection with a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay from nasopharyngeal swabs, that associated during the disease course persistent hiccup associated with the administration of cortisone therapy, dexamethasone.

Case report

We present the case of a 46-year-old Caucasian male, without comorbidities, non-smoker, who presented for admission into the Infectious Diseases Clinic of the Academic Emergency Hospital Sibiu, Romania 8 days after the onset of abdominal pain, accompanied after one day by dysphonia, headache, chills, low-grade fever, dry cough, insomnia, and inappetence. The patient was confirmed with SARS-CoV-2 infection by RT-PCR assay from nasopharyngeal swabs on the third day of disease onset. He was under treatment, self-medication, before his

Received: 22 October 2021; revised: 09 January 2022; accepted: 11 January 2021.

¹Assoc. Prof., MD, PhD, Lucian Blaga University of Sibiu, Faculty of Medicine Sibiu, Academic Emergency Hospital Sibiu - Infectious Diseases Clinic, Str. Lucian Blaga, Nr. 2A, Sibiu, 550169, Romania; ²MD, PhD, Children's Neurological Diseases Research Centre and Telemedicine (CEFORATEN) of the Paediatric Hospital Sibiu, Str. Pompeiu Onofreiu, Nr. 2-4, Sibiu, 550166, Romania.

*Corresponding author: Victoria Birluțiu, victoriabirlutiu@yahoo.com

Article downloaded from www.germs.ro

Published March 2022

© GERMS 2022

ISSN 2248 - 2997

ISSN - L = 2248 - 2997

admission into the hospital, from the fourth day of the disease evolution, with dexamethasone 10 mg 2 times per day orally, ivermectin 12 mg 1 time per day orally, enoxaparin 60 mg in 0.6 mL, 1 single dose syringe/day for subcutaneous administration, pantoprazole 40 mg/day orally, and paracetamol 500 mg orally as needed. The next day of treatment (day five since disease onset), the following changes were noticed by the patient: rebel hiccups, accentuated at night, associated with insomnia, and fatigue. During the next 3 days (day five to day eight since disease onset), the patient presented a fever of 38°C, dry cough, inappetence, the hiccup was accentuated and was not responsive to the administration of metoclopramide. The admission of the patient into the hospital was decided, laboratory changes suggesting an inflammatory syndrome. The pulmonary computerized tomography (CT) scan performed on day eight since disease onset revealed the following pathological changes: multiple areas of ground glass aspect, disseminated bilaterally, both peripherally, and also in upper lobes; alveolar consolidation areas that were occupying 5% of the right upper and left upper lobe and 25% of the left lower lobe respectively (Figures 1 and 2).

At the time of admission on physical examination, the following changes were noticed: 37.5°C fever, sweaty skin, dry cough, bilateral pulmonary crackles on auscultation, peripheral oxygen saturation 96% in ambient air and without the need of oxygen supplementation, heart rate of 104 beats per minute, and blood pressure 125 over 80 mmHg. Treatment with remdesivir was initiated consisting of a loading dose of 200 mg intravenously on the first day of admission, followed by 100 mg daily for the following 5 days, remdesivir being prescribed based on the available national guideline. Dexamethasone was replaced after 2 days from admission with methylprednisolone 250 mg/day intravenously for 3 days, under which the patient continued to show the same manifestations (accentuated nocturnal hiccup and fatigue) with a discrete improvement under treatment with intravenous metoclopramide 10 mg 3 times per day, intravenous ondansetron 4 mg 2 times per

day, and intravenous drotaverine hydrochloride 40 mg 3 times per day.

A decision to stop the administration of cortisone drugs was made, with the disappearance of the hiccup after 36 hours. The patient was discharged after 7 days, afebrile, without clinical respiratory or digestive manifestations. The most important laboratory studies are presented in Table 1.

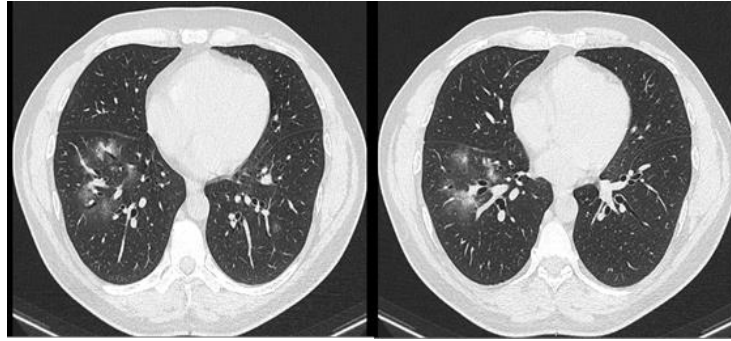
Discussion

Hiccup represents an involuntary way of paroxysmal movements in the inspiration action of the chest, associated with the contraction of the diaphragm and of the adjacent muscles and with the closure of the epiglottis.⁹

The causes of the hiccup, as a manifestation of the phrenic nerve irritation, may be associated with subphrenic hepatic abscess, pancreatitis, renal insufficiency, influenza, tuberculosis, alcohol consumption, gastric distension, reflux esophagitis,¹⁰ or with esophageal adenocarcinoma,¹¹ gastroduodenitis, and enteritis. Other cited causes associated with hiccup are: myocardial infarction,¹²⁻¹⁴ pulmonary embolism,¹⁵ cerebral tumors, meningitis, prostatic neoplasm,¹¹ idiopathic, and more recently, SARS-CoV-2 infection.^{8,16,17}

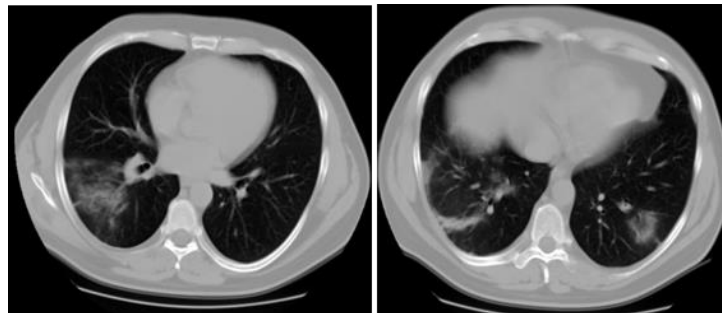
Few cases with hiccup associated with the SARS-CoV-2 infection have been reported to this point in the literature. The first case, described by Prince et al., is the case of a 62-year-old male known with diabetes mellitus and cardiovascular disease, that presented hiccup for 7 days and weight loss. Biologically he presented leukopenia, thrombocytopenia, hyponatremia, and hypochloremia.⁸

The second case¹⁷ was the case of a 48-year-old male, known with essential high blood pressure, hospitalized on the seventh day of hiccup, with pulmonary changes of bilateral basal subpleural opacity and crazy paving pattern. Among the laboratory examinations performed in this case, C-reactive protein was increased (51 mg/L), ferritin 2600 ng/mL, LDH 856 U/L. Under treatment with baclofen, the patient continued to present hiccups for another 7 days.



The pulmonary parenchyma presents ground glass opacities distributed at the level of the anterior and lateral segment of the right lower lobe, involving 5-25% (Severity Score 2).²¹ Ground glass opacity with round morphology in the apical segment of the upper left lobe and the lateral basal segment of lower left lobe (Severity Score 1+1).²¹

Figure 1. Sections of CT scan performed on day eight since disease onset



Peripheral progression of right lower lobe infiltrates now affecting approximately 26-49% of right lower lobe volume (Severity Score 3).²¹ Upper right lobe interest <5% (Severity Score 1)²¹ upper left lobe interest <5% (Severity Score 1),²¹ lower left lobe <5% (Severity Score 1).

Figure 2. Sections of CT scan performed on day eight since disease onset

Table 1

Laboratory test	Day 1 (third day since disease onset)	Day 8 (first day of hospitalization)
CRP (RV: 0-5 mg/L)	25.23	79.94
ASAT (RV: 0-35 U/L)	36	25
ALAT (RV: 0-49 U/L)	72	54
WBC (RV: 5-10 x10 ³ /UL)	5.91	11.23
Neutrophil-to-lymphocyte ratio	Not performed	6.3886
Ferritin (RV: 30-400 ng/mL)	Not performed	834.9
IL-6 (RV: 0-7 pg/mL)	Not performed	165.9
Fibrinogen (RV: 170-420 mg/dL)	Not performed	543.2
D-dimers (RV: 45-499 ng/mL)	Not performed	434.90
Fibrin monomers	Not performed	Negative
CPK (RV: 39-308 U/L)	Not performed	83

ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase; CPK – creatine phosphokinase; CRP – C-reactive protein; IL-6 – interleukin 6; RV – reference values; WBC – white blood cells.

The third case is described by Dorgalaleh, also a 52-year-old male, known with diabetes mellitus and congenital V-factor deficit,¹⁸ with a persistent hiccup, which the author associated in favor of epistaxis.

The case presented in this article is the case of a male patient without a past medical history, in which the hiccup occurred during treatment with dexamethasone and methylprednisolone,

and disappeared when this treatment was stopped.

From our experience, other cases of SARS-CoV-2 infection that we have been tracking during these months of the pandemic, with mild or severe forms of the disease, showed hiccup under dexamethasone treatment, an event also described in other medical conditions under the same treatment^{19,20} and improved at its cessation or when replaced by methylprednisolone.

Conclusions

All the cases described, with hiccup and SARS-CoV-2 infection presented so far have occurred in male patients, the case presented by us being the only one associated with the administration of dexamethasone to a patient without any comorbidity. Discontinuation of dexamethasone, and the use of metoclopramide, ondansetron or haloperidol may be beneficial in such disease conditions.

Ethics statement: The study was accepted by the Ethics, Medical Ethics and Deontology Committee of the Academic Emergency Hospital Sibiu 22893/2020/IX/22.

Consent: Written informed consent was obtained from the patient for publication of their case report and any accompanying images.

Availability of data: All data generated or analyzed during this case study are included in this published article.

Conflicts of interest: All authors – none to declare.

Funding: None to declare.

Authors' contributions: VB and CRS made contributions in equal parts to this manuscript in terms of acquisition, analysis, and interpretation of data, conception and design, and drafting the manuscript. VB designed the case study and coordinated data collection. VB was involved in providing the treatment for the patient and in collecting the data. Both authors were involved in revising the manuscript. Both authors read and approved the final version of the manuscript.

References

1. Birluțiu V, Birluțiu RM, Feiereisz AI. SARS-CoV-2 infection associated with micturition syncope: Our experience with 4 case reports. *Medicine (Baltimore)*. 2020;99:e21512.
<https://doi.org/10.1097/MD.00000000000021512>
2. Martín-Sánchez FJ, Del Toro E, Cardassay E, et al. Clinical presentation and outcome across age categories

among patients with COVID-19 admitted to a Spanish Emergency Department. *Eur Geriatr Med*. 2020;11:829-41.

3. Chen T, Hanna J, Walsh EE, Falsey AR, Laguio-Vila M, Lesho E. Syncope, near syncope, or nonmechanical falls as a presenting feature of COVID-19. *Ann Emerg Med*. 2020;76:115-7.
<https://doi.org/10.1016/j.annemergmed.2020.04.037>
4. Iancu GM, Solomon A, Birluțiu V. Viral exanthema as manifestation of SARS-CoV-2 infection: A case report. *Medicine (Baltimore)*. 2020;99:e21810.
<https://doi.org/10.1097/MD.00000000000021810>
5. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34:e212-3.
<https://doi.org/10.1111/jdv.16387>
6. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*. 2021;237:1-12.
<https://doi.org/10.1159/000512932>
7. Birluțiu V, Feiereisz AI, Oprinca G, et al. Cutaneous manifestations associated with anosmia, ageusia and enteritis in SARS-CoV-2 infection - A possible pattern? Observational study and review of the literature. *Int J Infect Dis*. 2021;107:72-77.
<https://doi.org/10.1016/j.ijid.2021.04.058>
8. Prince G, Sergel M. Persistent hiccups as an atypical presenting complaint of COVID-19. *Am J Emerg Med*. 2020;38:1546.e5-6.
<https://doi.org/10.1016/j.ajem.2020.04.045>
9. Budrewicz S, Góral M, Podemski R. [Pathophysiology and treatment of hiccup]. *Przegl Lek*. 2002;59:924-6.
10. Bryer E, Bryer J. Persistent postoperative hiccups. *Case Rep Anesthesiol*. 2020;2020:8867431.
<https://doi.org/10.1155/2020/8867431>
11. Arsanious D, Khoury S, Martinez E, et al. Ultrasound-guided phrenic nerve block for intractable hiccups following placement of esophageal stent for esophageal squamous cell carcinoma. *Pain Physician*. 2016;19:E653-6.
<https://doi.org/10.36076/ppj/2019.19.E653>
12. Krysiak W, Szabowski S, Stepień M, Krzywkowska K, Krzykowski A, Marciniak P. Hiccups as a myocardial ischemia symptom. *Pol Arch Med Wewn*. 2008;118:148-51.
<https://doi.org/10.20452/pamw.338>
13. Buyukhatipoglu H, Sezen Y, Yildiz A, Kucukdurmaz Z, Faruk O. Hiccups as a sign of chronic myocardial ischemia. *South Med J*. 2010;103:1184-5.
<https://doi.org/10.1097/SMJ.0b013e3181f4671e>
14. Gao H, Zhang B, Song L, Yao S, Zhang Z, Bai M. Acute proximal left anterior descending thrombosis manifested by persistent hiccups: A case report. *Medicine (Baltimore)*. 2019;98:e18096.
<https://doi.org/10.1097/MD.00000000000018096>
15. Hassen GW, Singh MM, Kalantari H, Yemane-Merriwether S, Ferrante S, Shaw R. Persistent hiccups as

-
- a rare presenting symptom of pulmonary embolism. West J Emerg Med. 2012;13:479-83.
<https://doi.org/10.5811/westjem.2012.4.6894>
16. Launois S, Bizet JL, Whitelaw WA, Cabane J, Derenne JP. Hiccup in adults: an overview. Eur Respir J. 1993;6:563-75.
 17. Bakheet N, Fouad R, Kassem AM, Hussin W, El-Shazly M. Persistent hiccup: A rare presentation of COVID-19. Respir Investig. 2021;59:263-5.
<https://doi.org/10.1016/j.resinv.2020.11.003>
 18. Dorgalaleh A, Dabbagh A, Tabibian S, Bahraini M, Rafieemehr H. Persistent hiccups in a patient with mild congenital factor V deficiency and COVID-19; clinical and laboratory finding of a rare bleeding disorder. Int J Lab Hematol. 2021;43:e87-8.
<https://doi.org/10.1111/ijlh.13385>
 19. Lee GW, Oh SY, Kang MH, et al. Treatment of dexamethasone-induced hiccup in chemotherapy patients by methylprednisolone rotation. Oncologist. 2013;18:1229-34.
<https://doi.org/10.1634/theoncologist.2013-0224>
 20. Kang JH, Hui D, Kim MJ, et al. Corticosteroid rotation to alleviate dexamethasone-induced hiccup: a case series at a single institution. J Pain Symptom Manage. 2012;43:625-30.
<https://doi.org/10.1016/j.jpainsymman.2011.04.011>
 21. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology. 2005;236:1067-75.
<https://doi.org/10.1148/radiol.2363040958>

Please cite this article as:

Birluțiu V, Șofariu CR. Association of hiccup and SARS-CoV-2 infection with the administration of dexamethasone: a case report. GERMS. 2022;12(1):107-111. doi: 10.18683/germs.2022.1312